In February 2008, FDA published the draft guidance, *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*. The draft was issued for comment and is intended to provide insight into what conditions make the dissemination of off-label information non-promotional and acceptable in the agency's view.1

The document addresses FDA's thoughts on "Scientific and medical information that concerns the safety or effectiveness of an approved drug or approved or cleared medical device for a new use that is not included in the product's approved labeling, or statement of intended uses,” distributed by manufacturers to healthcare professionals or healthcare entities.

Comments from my colleagues in response to the draft being circulated to team members outside the regulatory function, made me realize the importance of reiterating some basic terms to ensure the provisions laid out in the guidance are understood. At the risk of displaying a certain regulatory geekiness, let me clarify the many different ways the FDA uses the word “new.”

• A "new" drug is practically any drug, no matter how old it is. The phrase is used to exclude drugs that were on the market prior to 1938. But, FDA has recently explained that virtually all drugs, even old drugs, are not marketed in exactly the same form and with the same labeling as they were before 1938. So, even old drugs are "new.”

• In launching a product, FDA restricts the use of the term "new” in promotional labeling and advertising to the first six months after a product is marketed. After six months, it is no longer considered “new.”

• "New” uses are any uses not included in the product’s current labeling. Medical experts may have been using a product in a particular way for decades, but if it is not in the product’s labeling, the use is "new.”

It is these unapproved new uses that are the subject of this latest FDA draft guidance.

**The Basis for Scientific Exchange**

The guidance includes a number of positive, workable provisions. For instance, it states that scientific or medical information distributed should be accompanied by a representative publication that reaches contrary or different conclusions regarding the unapproved use, where such conclusions exist.

Another provision of the draft is that scientific or medical information distributed should be disseminated in conjunction with a representative publication that reaches contrary or different conclusions regarding the unapproved use, where such conclusions exist. This language simply requires the manufacturer to present the off-label use in its proper context, which also seems reasonable in the interest of scientific exchange.

**Let’s be Practical**

The draft also presents a number of difficulties. One key pragmatic issue is the provision that any scientific or medical reference publication distributed should not be written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer. It adds to this prohibition any publication that was edited or influenced by the manufacturer or anyone having financial ties to the manufacturer. These provisions disregard the reality that those individuals with an interest in a drug are the most likely to expend the effort to research the product and publish the data.

The guidance document language indicates FDA recognizes that off-label uses or treatment
Regimens may be important and may constitute medically recognized standards of care, and that the public health is advanced by allowing dissemination of such information. The restrictions on the involvement of those most knowledgeable about the product oppose those good intentions. FDA has the legal authority to determine whether distribution of information constitutes promotion of an unapproved "new use." To restrict the dissemination of truthful, scientific information simply on the basis of manufacturer involvement in its generation is unwarranted.

An additional provision that seems incongruous with the agency's intent is allowing reprints to be distributed at medical or scientific conferences in settings appropriate for scientific exchange but not in promotional exhibit halls or during promotional speakers' programs. This is inconsistent with other language that allows the reprints to be disseminated during promotional product details as long as the reprints are not physically attached to promotional material and are not the subject of discussion. FDA should not make speakers' programs more restrictive forums than a promotional product detail.

Clarification Required

A number of provisions in the draft guidance require clarification.

The document is intended to describe FDA's current thinking with regard to the distribution of scientific publications that discuss unapproved new uses for approved drugs. A footnote states that the draft guidance does not apply to scientific or medical information distributed in response to unsolicited requests. But it is less clear whether the scope includes other scientific venues. The specific reference to the suitability of supplying reprints at medical or scientific conferences implies that such activity is within the document's scope and highlights the ambiguity of the guidance's application to other scientific exchange under 21 CFR 312.7.

In addition, the requirement for publications to address adequate and well-controlled clinical investigations seems to specifically discount valuable information gathered from open-label, retrospective or pilot studies, as well as important ad hoc, subset analyses from studies based upon age, ethnicity, gender, or concomitant medication use that may provide useful information in small populations. Likewise, many studies examine several doses and/or regimens that were investigated in a clinical program. It is unclear whether FDA will consider an otherwise on-label description of a drug off-label due to the mention of additional treatment regimens contained within the study. FDA describes the importance of allowing manufacturers to disseminate truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs. The guidance includes in the meaning of the term "new use," not only off-label uses (meaning different indications), but also different dosage recommendations. It further states that the information contained in the publication should address adequate and well-controlled clinical investigations experts consider to be scientifically sound. These two statements effectively undermine the document's stated intent, which is to make available information that is in the interest of public health, and may even be the medically recognized standard of care. Information that is off-label only with respect to dosing recommendations should not be withheld from physicians simply because the data do not result from adequate and well-controlled studies. Some very significant and medically-sound emergency room practices rely upon data, that often develop from clinical practice trial-and-error and may be less rigorously generated than that from a phase 3 clinical program. Patients arriving in the emergency rooms across the US are treated based upon their physicians' access to this information for crises such as severe asthma, cerebrovascular accidents or myocardial infarctions.

Another issue to be clarified is the contradiction between the requirement that the scientific or medical information not be marked, highlighted, summarized or characterized by the manufacturer in any way, and the requirement that the publication display a permanently affixed statement disclosing the use's unapproved nature and any significant risks or safety concerns not discussed in the publication. It is unclear whether the reference to significant risks is intended only to highlight information that is different from the Warnings and Precautions applicable to the approved uses and documented in the product labeling. It would also be useful for the sponsor to describe the study design, including all prospectively identified endpoints, without reporting results or drawing conclusions, to place the study in the proper context for the reader.

The Regulatory Scheme and Politics

FDA publishes newly proposed regulations for
comment and often follows the same process for guidance documents as well. However, the reprint guidance first became public in a more unusual way. Representative Henry Waxman (D-CA) provided a draft to the press along with a copy of a letter he sent to the agency. In that letter, he railed against what he characterized as an opportunity for manufacturers to use abusive marketing practices that jeopardize safety, undermine public health and lead to unapproved uses of powerful drugs. Waxman outlined a list of concerns, including peer-reviewed articles he said are necessarily biased, which bias cannot be overcome with any inclusion of additional information or context. He also complained that the draft guidance provides a disincentive for manufacturers to study and gain approval for the new uses. Waxman cited previous concerns on FDA’s part about products that were believed to be safe and effective but were later shown to be ineffective or dangerous.

Although he raised some valid concerns, the solutions are subject to practical application. To be prevented from sharing what the data show now because we cannot know everything now, is not the answer. We must find the right balance to permit dissemination of what we are learning with the responsibility to share the information fairly and accurately. Waxman stated that the new draft guidance is an apparent attempt to displace Congress and establish, by administrative fiat, a new use of reprints that lacks sufficient safeguards. That statement gives insight into why the draft guidance was leaked to the press in advance of the FDA process and why Waxman so vigorously objected to it.

Interestingly, the generation of the draft guidance seems to have begun with a meeting held 13 April 2007 between FDA and representatives from Sidley Austin. The minutes of the meeting concluded that, with the sunset of the FDAMA 114 provisions, there is confusion about the rules regarding dissemination and guidance to clarify FDA’s current thinking would be helpful.

The document does not yet achieve that goal.

REFERENCES
3. 21 CFR 201.128, Meaning of Intended Use

AUTHOR
Kathleen Grim, RAC, is the Chairman of the RAPS Board of Editors for Regulatory Focus and the Executive Director of Regulatory Compliance at Sepracor, Inc. Her responsibilities include the regulatory review of advertising, promotion and scientific publications. She can be contacted at kathleen.grim@sepracor.com.